

# Ultra High-Field (7T) Magnetic Resonance Spectroscopy (MRS) in people with Amyotrophic Lateral Sclerosis (ALS)

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**Target Audience:** Neurologists, Neuroradiologists, MR Physicist, MR Spectroscopists

**Purpose:** Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disorder that predominantly affects the upper and lower motor neurons. The etiology of ALS is not very well understood but studies of the SOD1 rodent models of ALS suggest that glutamate excitotoxicity and neuroinflammation play an essential role in ALS progression. We studied brain metabolites changes that are related to these two mechanisms using ultra-high magnetic field (7-Tesla) magnetic resonance spectroscopy (MRS) in people with ALS.

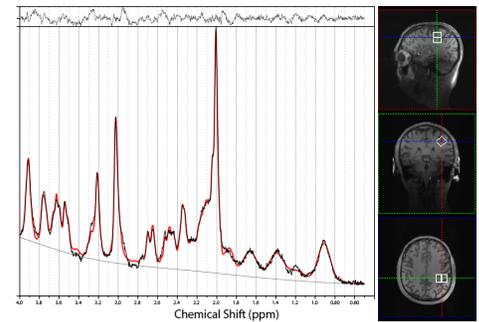
**Methods:** A total of nine patients with ALS and seven age-matched healthy controls were enrolled in the study. Of the 16 subjects eight ALS subjects (7 male, 53y ± 9y) and six healthy controls (3 male, 55.5y ± 12y) had good quality MRS data that were included in the analysis. All subjects had to be considered medically safe to tolerate MRI. Subjects were required to have a vital capacity (VC) ≥ 50% at screening. Clinical measures included disease duration, revised ALS Functional Rating Scale (ALSFRS-R), vital capacity, and reflex testing.

All in vivo MRI experiments were performed on a 7-Tesla MR imager (Siemens AG Erlangen) using a transmit birdcage coil and a 32-channel receive coil. Single voxel 1H MR spectra were acquired from the left motor cortex (VOI = 2 x 2 x 2 cm<sup>3</sup>) using an ultra short echo time MRS (SVS STEAM) with VAPOR (Variable Power RF pulses and Optimized Relaxation Delays) water suppression. Ultra short echo times of 5 ms were used to reduce T2 relaxation effects and J-modulation. High bandwidth slice selective RF pulses were used to minimize chemical shift displacement errors. Other parameters included TR = 5000 ms, TM = 45 ms, 96 averages, bandwidth 4k, no outer volume saturation was used). A loop routine prior to data acquisition was used to for parameter optimization to maximize spectral quality. In addition, water unsuppressed spectra were acquired to estimate absolute concentrations.

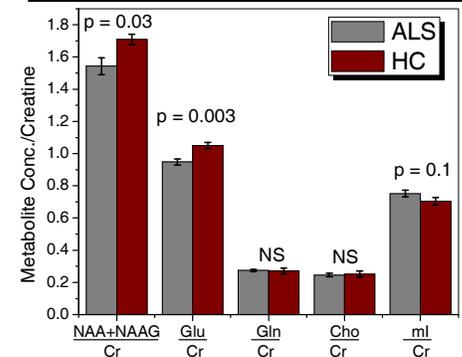
Metabolite quantification was performed with LCModel for the following metabolites: Creatine + Phosphocreatine (Cr), Glutamate (Glu), Glutamine (Gln), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), myo-Inositol (mI), and choline-containing compounds (Cho). Figure 1 shows a typical spectrum including the fit provided by LCModel. For statistical data analysis, Student t-tests were used to compare metabolite concentrations between ALS subjects and healthy controls and Spearman correlation coefficients were calculated to estimate the correlations between MRS metabolites and clinical outcomes.

**Results:** The comparison between ALS patient and healthy controls revealed a decrease (p=0.03) in NAA+NAAG/Cr in people with ALS compared to healthy controls (HC) (Figure 2). In addition, we identified whether changes in NAA+NAAG and/or Cr are responsible for the changes observed in the ratio, and found a decrease in NAA+NAAG (p=0.02) in people with ALS compared to HC and no differences in Cr (p = 0.21). Furthermore, we separated differences in NAA and NAAG between ALS and HC subject and found both metabolite concentrations to be decreased (P = 0.03 and P = 0.04, respectively). Glutamate (p = 0.03) as well as Glu/Cr (p = 0.003) were decreased in people with ALS compared to HC, while neither Gln (p = 0.6) nor Gln/Cr (p = 0.8) were altered in ALS. No difference in Cho/Cr was observed (p = 0.7). Interestingly, mI/Cr was increased in people with ALS compared to HC (p=0.1).

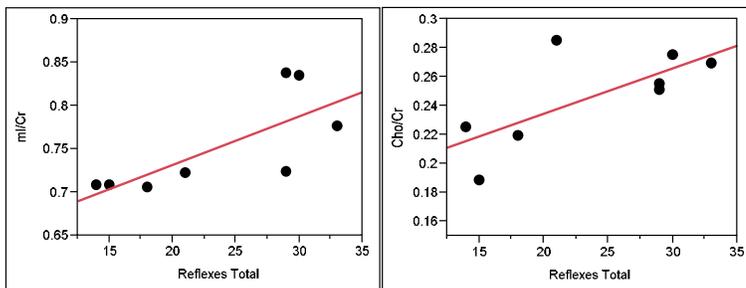
Furthermore, certain clinical outcomes were collected for each ALS subject to assess disease progression; these included Vital Capacity (VC 86% ± 20.6) ALSFRS (37 ± 4.9) Reflex total (23 ± 7.2) and time from diagnosis to scanner (17 months ± 18.4). we performed correlations between clinical measures and spectroscopic markers (Figure 3): mI/Cr was positively correlated with increased reflexes (R<sub>p</sub> = 0.80, p=0.02) and also Cho/Cr was positively correlated with increased reflexes (R<sub>p</sub> = 0.66, p=0.07).



**Figure 1:** An example spectrum including placement of the VOI on the left motor cortex



**Figure 2:** Metabolite concentrations/creatine in ALS subjects vs. healthy controls



**Figure 3:** mI/Cr (left) and Cho/Cr (right) were both positively correlated with increased reflexes (R<sub>p</sub> = 0.80, p=0.02 and R<sub>p</sub> = 0.66, p=0.07, respectively).

**Conclusion:** In conclusion, MRS is a promising tool to study molecular changes in people with ALS and longitudinal MRS studies are needed to better characterize these molecular changes as the disease progresses over time.

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**Discussion:** Our finding of decreased NAA/Cr in ALS is suggestive of neuronal loss in the motor cortex and is consistent with ALS pathology and previous 1.5T and 3T MRS studies in ALS. Contrary to our initial hypothesis, we saw a decrease in glutamate in the ALS group without significant changes in Glutamine. One of the limitations of MRS is the inability to differentiate intra- from extra-cellular metabolites changes, suggesting that the decrease in glutamate might be secondary to the loss of intracellular glutamate due to neuronal degeneration. Interestingly, we saw a trend for increased mI/Cr in the ALS group suggesting increased glial proliferation and inflammation in the motor cortex. Furthermore, the increase in mI/Cr strongly correlates with pathological reflexes, a clinical marker of upper motor neuron degeneration. In addition, Cho/Cr, another inflammatory marker correlates with pathological reflexes. These findings are consistent with the increase of activated microglia around motor neurons seen in ALS postmortem tissue and rodent pathological studies.